RESPONSIBLE INNOVATION IN DIETARY SUPPLEMENTS

PROMOTING OVERALL COMPLIANCE WITH THE PREMARKET NOTIFICATION REQURIEMENT THROUGH ENFORCEMENT

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UNRESOLVED NDI TOPICS

- Grandfathered List of Old Dietary Ingredients
- NDI Master File
- IP Protection
- Chemically Altered
- Broad vs. Limited Scope of 201(ff)(1)(E)
- Synthetic Copies of Botanical Constituents
- NDI Enforcement (Silence on Sticks, Movement to Carrots)
- Food Additive Level of Testing
- Economic Impact Analysis
- FDA's 2nd Chance to Opine on an NDI (Vinpocetine Administrative Proceeding)

NDI TOPICS LEFT UNRESOLVED

- **Grandfathered List of Old Dietary Ingredients**
  - Public meeting held on this topic
  - NPA created this book in 2017 with references to advertisements
  - No statements provided by FDA regarding recognition of a grandfathered list
  - Discussion tabled
- **NDI Master File List**
  - Public meeting held on this topic
  - Discussion on NDI Master File has been shelved
  - Agency has no agreement on how to define it
  - Could solve NDI enforcement issues
- **IP Protection**
  - Was not discussed in NDI Draft Guidance
- **Chemically Altered**
  - To be dealt with May 16 at FDA Public Meeting (discussed at meeting)
- **Broad/Limited Scope of 201(ff)(1)(E)**
  - To be dealt with May 16 at FDA Public Meeting
- **Synthetics of Botanicals**
  - To be dealt with May 16 at FDA Public Meeting
- **Food Additive Level of Testing**
  - Cost is a concern
- **NDI Enforcement**
  - Reliance on ‘carrots’ vs. ‘sticks’, future shift away from ‘sticks’ and toward ‘carrots’??
- **Economic Impact Analysis**
  - Was never done
- **FDA’s second chance to opine on an NDI**
  - Vinpocetine Administrative Proceeding (has not been removed)

NDI NOTIFICATION

INSIDER LAW

FDA, supplement industry eye ways to foster compliance with ingredient notification system

FDA is looking at ways to foster the submission of new dietary ingredient notifications. The notification system, established by law in 1994, may be in need of changes to ensure U.S. regulators have an opportunity to review the safety of new ingredients before they are marketed in supplements.

Total number of notifications submitted last fiscal year to FDA to establish safety of NDI in Dietary Supplements

45

https://www.naturalproductsinsider.com/ingredients/fda-supplement-industry-eye-ways-foster-compliance-ingredient-notification-system

NDI NOTIFICATION ISSUES

Inadequate enforcement

- FDA should provide incentives to comply with (a requirement in a 25-year-old law) because FDA currently is not providing adequate enforcement to give companies an incentive to file.
- a lack of enforcement by the FDA on NDIs

A disconnect

- disconnect between the way firms are filing NDI notifications and our ability to comprehensively police the market
- FDA's ability to police the market "in a way that is both resource-efficient and consistent with the goals of protecting the public health."

UNRESOLVED NDI TOPICS:
NDI Enforcement

New Dietary Ingredient Notification

What Does it Buy You?

- By notifying the Agency, the burden is on FDA to show that it is unsafe
- Without Notifying the Agency, the DS can be adulterated for failure to submit an NDI notification + lack of safety data
- Just need to show “reasonable expectation of safety”

UNRESOLVED NDI TOPICS:
NDI Enforcement

Knockoff ingredients

- A recurring frustration for industry: so-called knockoff or copycat ingredients that purport to be identical to NDIs that have invested in the notification process but don't have a relationship with the notifier.
- If a copycat ingredient isn’t on such a list, FDA could place it on an import alert or bulletin

Import Alerts

Import Alert Number	Import Alert Type	Publish Date	Import Alert Name
54-07	DWPE	04/23/2019	"Germanium Products"
54-08	DWPE	03/21/2018	"Detention Without Physical Examination of Dried Bulk Plantain Due To The Presence Of Digitalis"
54-10	DWPE	04/23/2019	"Detention Without Physical Examination of Bulk/Finished Dietary Supplements Products Containing Aristolochic Acid"
54-11	DWPE	09/15/2015	"Detention Without Physical Examination of Bulk Dietary Ingredients And Dietary Supplements Containing Androstenedione"
54-12	DWPE with Surveillance	09/15/2015	"Detention Without Physical Examination of Foods Labeled As Being Or Containing Siberian Ginseng"
54-13	DWPE	10/05/2017	"Detention Without Physical Examination of Dietary Supplements And Bulk Dietary Ingredients Containing Ephedrine Alkaloids From All Countries"
54-14	DWPE	03/18/2019	DETENTION WITHOUT PHYSICAL EXAMINATION OF DIETARY SUPPLEMENT PRODUCTS FROM FIRMS WHICH HAVE NOT MET DIETARY SUPPLEMENT GMPS
54-15	DWPE	12/20/2016	DETENTION WITHOUT PHYSICAL EXAMINATION OF DIETARY SUPPLEMENTS AND BULK DIETARY INGREDIENTS THAT ARE OR CONTAIN MITRAGYNA SPECIOSA OR KRATOM
54-16	DWPE	04/23/2019	"DETENTION WITHOUT PHYSICAL EXAMINATION OF PRODUCTS THAT ARE MARKETED AS FOODS, INCLUDING PRODUCTS MARKETED AS DIETARY SUPPLEMENTS, THAT CONTAIN AN ACTIVE PHARMACEUTICAL INGREDIENT"
54-17	DWPE	03/21/2018	DETENTION WITHOUT PHYSICAL EXAMINATION OF DIETARY SUPPLEMENTS DUE TO LEAD, ARSENIC, MERCURY, AND/OR CADMIUM CONTAMINATION

Import Alerts

IA 54-11 references NDIs

Reason for Alert:

FDA is not aware of any information demonstrating that androstenedione was lawfully marketed as a dietary ingredient in the United States before October 15, 1994. Nor is FDA aware of any information demonstrating that this ingredient has been present in the food supply as an article used for food in a form in which the food has not been chemically altered. In the absence of such information, androstenedione is subject to the notification requirement for a new dietary ingredient in 21 U.S.C. 350b(a)(2) and 21 CFR 190.6. FDA has not received any such notifications.

Import Alerts

IA 54-14 Import alert for not meeting DS GMPs. The others are not GMP related

Reason for Alert:

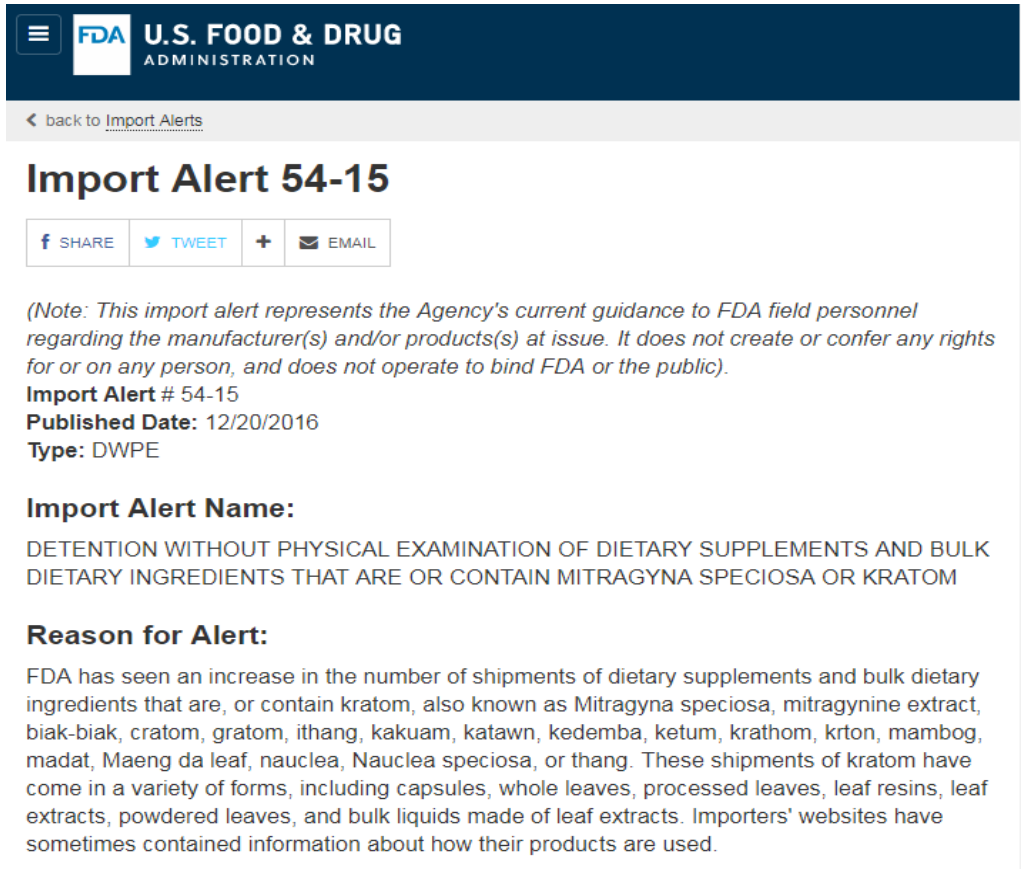
Section 402(g)(2) of the Federal Food, Drug, and Cosmetic Act provides, in part, that the Secretary of Health and Human Services may, by regulation, prescribe good manufacturing practices (GMP) for dietary supplements. On June 25, 2007, FDA published a final rule setting out the GMP requirements for dietary supplements in the Federal Register [72 FR 34942].

The final rule created Title 21, part 111 (21 CFR Part 111), which establishes the minimum current GMPs necessary for activities related to manufacturing, packaging, labeling, or holding dietary supplements to ensure the quality of the dietary supplement. Per the regulation, quality means that the dietary supplement consistently meets the established specifications for the identity, purity, strength, and composition. Any dietary supplement imported or offered for import into the United States is subject to the aforementioned regulation.

FDA performs foreign inspections of dietary supplement manufacturers to determine compliance with the regulation. FDA may detain affected products if inspection has revealed that a firm is not operating in conformity with current good manufacturing practices (GMP's).

When, and if, FDA confirms that corrections have been made, the respective firm's dietary supplement products will be removed from detention without physical examination.

Import Alert 54-15:
Mitragyna speciosa (Kratom)



FDA U.S. FOOD & DRUG ADMINISTRATION

back to Import Alerts

Import Alert 54-15

SHARE TWEET + EMAIL

(Note: This import alert represents the Agency's current guidance to FDA field personnel regarding the manufacturer(s) and/or products(s) at issue. It does not create or confer any rights for or on any person, and does not operate to bind FDA or the public).

Import Alert # 54-15
Published Date: 12/20/2016
Type: DWPE

Import Alert Name:

DETENTION WITHOUT PHYSICAL EXAMINATION OF DIETARY SUPPLEMENTS AND BULK DIETARY INGREDIENTS THAT ARE OR CONTAIN MITRAGYNA SPECIOSA OR KRATOM

Reason for Alert:

FDA has seen an increase in the number of shipments of dietary supplements and bulk dietary ingredients that are, or contain kratom, also known as Mitragyna speciosa, mitragynine extract, biak-biak, cratom, gratom, ithang, kakuam, katawn, kedemba, ketum, krathom, krton, mambog, madat, Maeng da leaf, nauclea, Nauclea speciosa, or thang. These shipments of kratom have come in a variety of forms, including capsules, whole leaves, processed leaves, leaf resins, leaf extracts, powdered leaves, and bulk liquids made of leaf extracts. Importers' websites have sometimes contained information about how their products are used.

https://www.accessdata.fda.gov/cms_ia/importalert_1137.html

Import Alert 54-15:
Mitragyna speciosa (Kratom)

specifically references NDIs and failure to file.

Kratom is a botanical that qualifies as a dietary ingredient under section 201(ff)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321(ff)(1)]. When marketed as a dietary ingredient, FDA also considers kratom to be a new dietary ingredient under section 413(d) of the Act [21 U.S.C. 350b(d)] because, to the best of the agency's knowledge, there is no information demonstrating that this substance was marketed as a dietary ingredient in the United States before October 15, 1994.

Furthermore, based on FDA's review of the publicly available information regarding kratom, there does not appear to be a history of use or other evidence of safety establishing that kratom will reasonably be expected to be safe as a dietary ingredient. In fact, the scientific literature disclosed serious concerns regarding the toxicity of kratom in multiple organ systems. Consumption of kratom can lead to a number of health impacts, including respiratory depression, nervousness, agitation, aggression, sleeplessness, hallucinations, delusions, tremors, loss of libido, constipation, skin hyperpigmentation, nausea, vomiting, and severe withdrawal signs and symptoms. In the absence of a history of use or other evidence of safety establishing that kratom will reasonably be expected to be safe as a dietary ingredient, kratom and kratom-containing dietary supplements and bulk dietary ingredients are adulterated under section 402(f)(1)(B) of the Act [21 U.S.C. 342(f)(1)(B)], because they contain a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury.

Natural Alternatives' CarnoSyn® Beta-Alanine Receives New Dietary Ingredient Status From The FDA

One of Bell's clients—NAI—is developing a multi-pronged strategy to protect its NDI investment and hold others accountable for non-compliance with the law. Bell suggested the strategy includes working with federal agencies like FDA and U.S. Customs and Border Protection.

"We're working on a pretty broad strategy on how to assist in enforcement of that [NDI], and compliance is what we're really looking for," the lawyer said.

Knockoff ingredients not only threaten to undermine the investments of companies that submitted an NDIN, they pose possible safety concerns. Although the knockoff ingredients may purport to be the same material as an ingredient subject to an NDIN, "we don't know that they're equivalent," Fabricant observed. "We don't have peace of mind with them."

Failure of those ingredients to notify FDA, he added, "just disincentivizes everybody in the whole process."

Proposed Import Alert
IA 54-18: For other NDIs

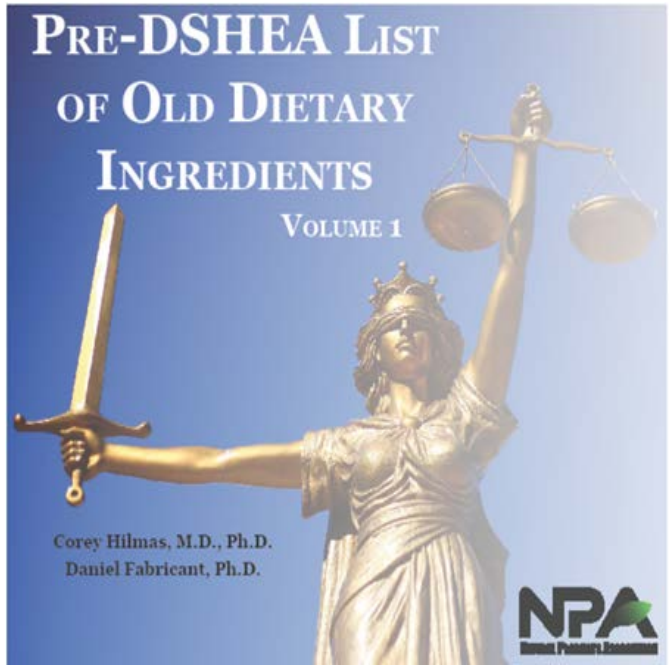
NPA proposal to submit import alert for other NDIs

UNRESOLVED NDI TOPICS:
Grandfathered List of Old Dietary Ingredients

On October 3, 2017, FDA held a public meeting to discuss the development of a list of Pre-DSHEA Dietary Ingredients. (FDA is not required to put together list of ODI)

NPA's Pre-DSHEA List of Old Dietary Ingredients Book

- First pre-DSHEA ODI list to be published and available to the public.
- Created with independent & verifiable sources
- These ingredients would be exempt from filing notification with FDA as New Dietary Ingredients
- Includes ingredients submitted as GRAS notices to FDA with no further comment by the Agency.
- Met with and notified the Agency of NPA's ODI book.



UNRESOLVED NDI TOPICS:
NDI Master File

Master File – *akin to drug master file, this system would eliminate the need for unnecessary duplicate filings of the same NDI and include clarification on allowance for easy, follow-on notifications involving previously submitted evidence*

- Win “sort of” for the industry; however, this was always going to be acceptable

UNRESOLVED NDI TOPICS:
NDI Master File

Providing Incentives Through 'Master Files'

Industry sources have envisioned a concept in which an ingredient manufacturer grants its customers—manufacturers of finished brands, for example—permission to rely on an NDIN in a "master file" accessible to FDA.

An anticipated caveat: Distributors and manufacturers listed in a master file would be required to follow the manufacturing processes, identity specifications, dosage limits and other criteria spelled out in the original notification to FDA that was acknowledged in a letter without an objection. (Industry sometimes described such FDA acknowledgments as "good day letters").

If FDA is going to address master files in a final guidance, it must also be enforced.

UNRESOLVED NDI TOPICS:
IP Protection

IP Protection – *discourage copy-cat ingredients entering the marketplace without an active NDI on file. If you can't protect IP, why should firms file NDIs?*

- *THIS WAS NOT ADDRESSED in the NDI GUIDANCE*

UNRESOLVED NDI TOPICS:
Chemically Altered

Chemically Altered – *a listing of chemical processes that would and would not lead to a "chemically altered" ingredient and clarification over what is meant by "present in the food supply in a form not chemically altered."*

- *FDA's reliance on Congressional Record (Leg. History)*
- *THIS WAS NOT ADDRESSED in the NDI GUIDANCE*
- *NPA Asked for an illustrative list of processes which do not lead to a "chemically altered" ingredient (ie. esterification)*

UNRESOLVED NDI TOPICS:
Food Additive Level of Testing

Food Additive Level of testing – further attempts by FDA to blur the line between NDIs/FAP

AGENCY:

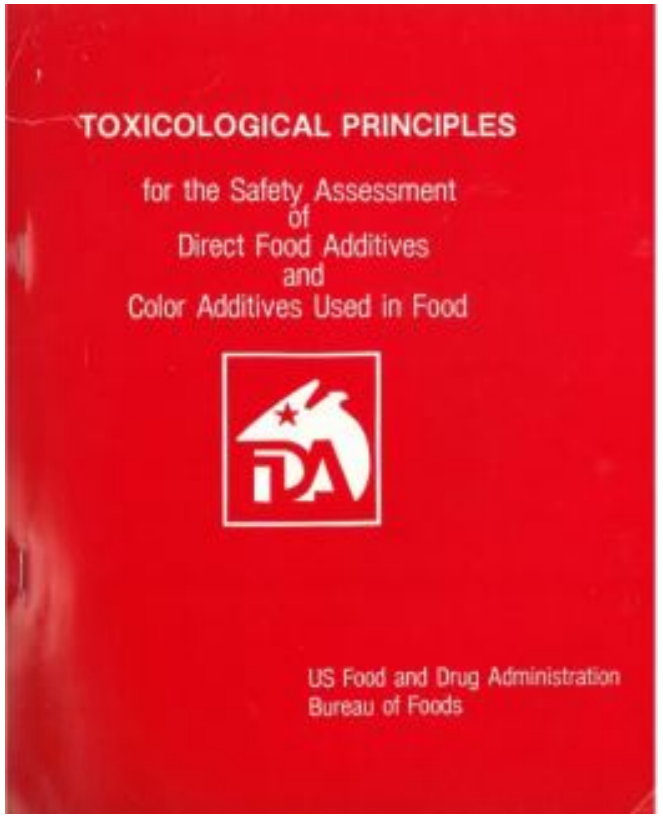
Food and Drug Administration, HHS.

ACTION:

Notification of public meeting; request for comments.

SUMMARY:

The Food and Drug Administration (FDA or we) is announcing a public meeting to solicit comments on certain topics related to our guidance titled "Toxicological Principles for the Safety Assessment of Food Ingredients," known less formally as the "Redbook." The purpose of our public meeting is to invite public input into possibly expanding the scope of the Redbook to include chemical safety assessments for all products over which FDA's Center for Food Safety and Applied Nutrition (CFSAN) has statutory authority including regulatory contexts such as food additives, food contact substances, dietary supplement ingredients, food contaminants, and cosmetics. The Redbook would describe toxicological principles which apply across regulatory categories while still providing specific guidance for applying these principles within each particular context. The safety of foods containing microbial contaminants will continue to remain outside of



UNRESOLVED NDI TOPICS:
Economic Impact Analysis

Never considered in the NDI Re-Draft

◦ Toxicology Studies	$178,000-$328,000
◦ FTE & Consultants for preparing NDI submission	$162,500
◦ Analytical & Physical Properties	$ 27,500

THANK YOU

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